IN THE DRAWINGS:

The attached sheets of drawings include changes to FIGS. 19, 21A, 21B, and 24. Sheets 19, 22, 23, and 27 replace the previous drawing sheets submitted for these figures. The "TM" symbol has been added. (See attached Replacement Sheets and Annotated Sheets showing changes.)

REMARKS

The Office Action mailed March 29, 2006 has been received and reviewed. The application is to be amended as previously set forth. Claims 1, 8-10, 17 and 21 have been amended. Claims 2-6 are to be canceled. Claim 30 is new. Claims 11-16, and 21-29 were previously withdrawn. No new matter has been added. All amendments and cancellations are made without prejudice or disclaimer. Claims 1-10 and 17-20 are currently under examination. All stand rejected. Reconsideration is respectfully requested.

Interview Summary

Applicants would first like to thank the Examiner and his supervisor for the courtesy extended to applicants' representatives at the personal interview of May 15, 2005. Pursuant to MPEP § 713.04, applicants state the following:

Applicants' representatives discussed the rejections under 35 U.S.C. § 102 and 103. Applicants' representatives explained why claims 1, 3-9, and 18 are novel over Fallaux et al., and claims 1-10, and 17-20 are non-obvious over Fallaux et al. in view of Dorai et al. It appeared that the examiners followed the rationales of applicants' representatives', and agreed that the claims would overcome the rejections of record if claim 1 is amended to incorporate the limitations of claims 2 and 6. Applicants' representatives also discussed the rejections under 35 U.S.C. § 112. The examiner agreed that the term "human protein" is clear and definite. With respect to the specification, applicants' representatives agreed to add the trademark symbol ™ for all occurrences of PER.C6 cells.

Basis for new claims

Claim 30 has been added, wherein the protein of interest is specified as being a glycoprotein. Basis for the new claim can be found throughout the specification, *e.g.*, in paragraphs **[0006]**, **[0051]**, and **[0095]** of the specification, and hence no new matter is added by this new claim.

Election/restrictions

Claims 11-16, and 21-29 were withdrawn from consideration. Applicants respectfully

request rejoinder of the methods claims once the product claims have been allowed.

The presently claimed cells are useful 'intermediates' in the production of recombinant proteins by methods using the cells as disclosed in the application, and hence the cells are claimed separately (*i.e.* not in the form of method claims). It is clearly the intention of the applicants to rejoin the withdrawn method claims (that include a further step of harvesting the protein of interest from the cell or the suitable medium, and hence are even further distinguishing from the Fallaux et al. reference by that additional feature), and claim 21 has been amended to incorporate the limitations of claim 1.

Information Disclosure Statements

It was asserted that the Information Disclosure Statements filed on 1/17/2006 and 5/26/2005 did not comply with 37 CFR 1.98(a)(2).

It is respectfully submitted that the IDS filed on 5/26/2005 complies with 37 CFR 1.98. "Pursuant to 37 C.F.R. § 1.98(d), a copy of any patent, publication or other information listed in the Information Disclosure Statement is not required to be provided if it was previously cited by or submitted to the office in a prior application, provided that the prior application is properly identified in the statement and relied upon for an earlier filing date under 35 U.S.C. § 120. Accordingly, no copy of information marked with a pound sign (#) is enclosed because it was previously cited or submitted to the patent office in a prior application which is properly identified above, and is relied upon for an earlier filing date." (IDS, filed on 5/26/2005, at page 1-2). All of the cited foreign patent documents and non-patent literature were previously submitted to the Office in the prior application Serial No.: 09/549,463, filed on September 3, 2002, for "RECOMBINANT PROTEIN PRODUCTION IN A HUMAN CELL", which application is being relied upon for an earlier filing date under 35 U.S.C. § 120.

Applicants believe that the supplemental IDS filed on 1/17/2006 was also in compliance with 37 CFR 1.98. However, to expedite prosecution, the reference not yet considered by the Examiner (CARAVOKYRI et al., "Constitutive Episomal Expression of Polypeptide IX (pIX) in a 293-Based Cell Line Complements that Deficiency of pIX Mutant Adenovirus Type 5," Journal of Virology, November 1995, pp. 6627-6633, Vol. 69, No. 11.) is included in the supplemental IDS enclosed herewith, and a copy of the reference is also enclosed.

Specification Objection

The disclosure was objected to because of an informality. The specification and drawings have been amended herein to include the appropriate trademark symbols. Claim 9 has been amended to include a trademark symbol.

The Office states that the Trademark PER.C6™ should be accompanied by generic terminology. Generic terminology, such as "human embryonic retinoblast cell line containing in its genome human adenovirus type 5 (Ad5) E1A and E1B coding sequences (nt. 459-3510) under the control of the human phosphoglycerate kinase (PGK) promoter", has been provided for PER.C6™ at its first occurrence, *i.e.* paragraph **[0036]** of the specification. To avoid a lengthy repeat of the generic terminology at every occurrence of PER.C6™, applicants believe that PER.C6™ itself should be sufficient, as also known to a person with ordinary skill in the art. Accordingly, applicants believe the amended specification is clear.

Claim Objections

Claims 8 and 17 were objected to because of an informality. Claims 8 and 17 have been amended to include the full descriptions for "PGK" and "CMV", respectively.

Claim rejections - 35 U.S.C. § 112

Claims 1-10, and 17-20 stand rejected under 35 U.S.C. 112, second paragraph, for reciting the term "proteinaceous substance". Although applicants respectfully disagree with the Examiner and submit that the term is clear and definite as being defined in paragraph **[0010]** of the specification, the term has been amended in the claims into "protein of interest", to speed up the prosecution. It is submitted that the term "protein" is clear and definite. Since claim 1 already contains the term "protein" in the context of E1A and E1B, the recitation "of interest" has been added for the protein that is to be recombinantly produced with the cells, to provide antecedent basis for the dependent claims (*e.g.*, claims 10, 17, 30).

Claim 10 stands rejected under 35 U.S.C. 112, second paragraph, for reciting the term "human protein", which the Examiner thought unclear. Applicant respectfully disagrees, and believes the term is clear in view of the specification and the knowledge of a person with

ordinary skill of the art. It is clear from the specification that a protein that comprises a naturally-occurring human sequence is intended to be included within the scope of the invention, *e.g.*, the exemplified human erythropoietin protein. Such human proteins can, for instance, be administered to humans after having been produced according to the methods of the invention, see *e.g.*, paragraph [**0011**]. As discussed during the interview, the term "human protein" therefore is clear, and reconsideration is respectfully requested.

Claim 9 stands rejected under 35 U.S.C. 112, first paragraph for allegedly failing to comply with the enablement requirement. A duly executed Budapest Treaty declaration with the deposit receipt is enclosed herewith to overcome this rejection. Reconsideration is respectfully requested.

Double patenting

Claims 1-10, 17, and 18 were provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-7 and 9-11 of copending Application No. 10/644,256.

Claims 1-10, 17, and 18 were provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 10-19, 21-35, 41, and 42 of copending Application No. 10/234,007.

Claims 1-10, 17, and 18 were provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 14, 15, 18, and 19 of copending Application No. 11/271,090.

Claims 1-10, 17, and 18 were provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-6 of copending Application No. 10/499,298.

Claims 1-10, 17, and 18 were provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 42-49 of copending Application No. 11/026,518.

To expedite prosecution, a terminal disclaimer is enclosed herewith to overcome the provisional nonstatutory obvious type double patenting rejection, over copending applications 10/644,256; 10/234,007; 11/271,090; 10/449,298 and 11/026,518.

Claims 1-10, 17, and 18 were provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 28, 29, 31-40, and 43-50 of copending Application No. 11/039,767.

Claims 1-10, 17, and 18 were provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 37-39 of copending Application No. 10/497,832.

Copending application No. 11/039,767 was filed January 18, 2005. Copending application No. 10/497,832 was filed January 10, 2005. The present application was filed earlier than both of these two applications. The conflicting claims in application No. 11/039,767 or application No. 10/497,832 have not in fact been patented. Applicants will address these issues in the conflicted applications if required, once the present claims have otherwise been found patentable.

Furthermore, MPEP §804 provides:

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

Accordingly, in view of the amendments and further arguments provided herewith, if the provisional nonstatutory double patenting rejections are the only remaining rejections in the present application, the rejections should be withdrawn to allow the present application to issue as a patent.

Claim rejections - 35 U.S.C. § 102

Claims 1, 3-9, and 18 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Fallaux et al. (WO 97/00326) (hereinafter "Fallaux et al."). Applicants respectfully traverse these rejections.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single reference which qualifies as prior art under 35 U.S.C. § 102. *Verdegaal Brothers v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053

(Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claim 1 has been amended to include the elements of claim 2, such that the recombinant nucleotide sequence encoding the protein of interest has been integrated into the genome of the cell, so that it forms part of the genome of the cell.

Fallaux et al. on page 28 lines 1-9, mentions β-galactosidase and thymidine kinase as proteins (Office Action page 24 lines 1-2), but it is submitted that it does so as part of an adenoviral vector only (*i.e.* the DNA encoding these proteins is included in the genome of the adenoviral vector, in place of the deleted E1 gene thereof). Briefly, (i) claim 1 specifically excludes a eukaryotic cell that expresses an adenoviral structural protein, and (ii) claim 1 as amended contains the limitation that the nucleotide sequence encoding the protein of interest forms part of the genome of the cell, in contrast to an adenovirus (an adenovirus does not integrate into the genome, see, *e.g.*, Fallaux et al., page 5 line 10). Hence, the passage does not anticipate the present claims.

Fallaux et al. further discloses on page 31 line 25 to page 32 line 2 that the cells therein (including PER.C6™ cells) were transfected with foreign DNA, using the *E. coli* β-galactosidase-encoding lacZ gene as a reporter. However, the transient transfections described therein did not include integration of the reporter gene into the genome of the cells, and therefore the disclosures therein do not anticipate amended claim 1.

Applicants believe that the amended claim 1, which incorporates the elements of claim 2, is not anticipated by Fallaux et al., as also evidenced in the Office Action that claim 2 was not rejected under 35 U.S.C. § 102 over Fallaux et al. Further, the Office Action states that "Fallaux et al. do not teach such a cell wherein the recombinant nucleotide sequences in expressible format encoding the proteinaeous substance forms part of the genome of eukaryotic cell." (Office Action at page 26, first sentence of second paragraph). As such, claim 1 is not anticipated by Fallaux et al.

Claims 3-6 have been canceled rendering the rejections as to them moot.

Claims 7-9, and 18 are not anticipated by Fallaux et al. for, *inter alia*, depending from claim 1 which is not anticipated.

Claim rejections - 35 U.S.C. § 103

Claims 1-10 and 17-20 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Fallaux et al. in view of Dorai et al. (U.S. Patent 5,631,158) (hereinafter "Dorai et al."). Specifically, it was thought that Fallaux et al. does not teach a cell wherein the recombinant nucleotide sequence in expressible format encoding the proteinaceous substance forms part of the genome of the eukaryotic cell. It was further thought that Fallaux et al. does not teach such a cell wherein the proteinaceous substance is a human protein. Nor does Fallaux et al. teach such a cell in culture, wherein the cell culture is a suspension culture, or wherein the suitable medium is free of animal- or human-derived serum and animal- or human-derived serum components. It was alleged that Dorai et al. teaches the above. Applicants traverse these rejections as hereinafter set forth.

The standard for establishing and maintaining a rejection under 35 U.S.C. § 103(a) is set forth in M.P.E.P. § 706.02(j), which provides:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

No suggestion or motivation exists to modify or combine the reference teachings

The current application relates to the production of recombinant proteins, using methods being suitable for large scale production. As is clear from the specification, processes for recombinant protein production in mammalian cells were known prior to the present invention. Such processes generally entailed providing a cell with a gene encoding a recombinant protein, culturing the cell in a suitable medium and harvesting the recombinant protein from the cell and/or the medium. A widely used host cell for this purpose was (and still is) a Chinese hamster ovary (CHO) cell, but other cell types had also been used. Among other things, the present application describes a particularly useful process, wherein a new cell type, *viz.* a cell that

contains genetic information encoding adenoviral E1A and E1B and which cell is derived from a human embryonic retinoblast (HER), is used for recombinant protein production. Such cells had not been described or even remotely suggested as being useful for protein production prior to the present invention. It is the merit of the present invention to, for the first time, describe the novel and inventive use of this cell type for the purpose of recombinant protein production, and showing that this cell type is very suitable for this process.

In contrast to the present application, Fallaux et al. relates to the field of gene therapy using materials derived from recombinant adenovirus. In particular, when E1-deleted adenoviruses are to be produced, they need to be complemented for their loss of the essential E1-functions. Therefore, E1 is generally provided *in trans*, by expressing E1 from so-called packaging cells, wherein the E1-deleted adenovirus can then be propagated. The most well-known and widely used packaging cells prior to Fallaux et al. were the HEK293 cells. One particular problem using the 293 cells was that recombination between the genome of the packaging cell and the E1-deleted adenovirus vector genome was possible, because of overlap between E1 sequences present in the genome of the 293 cells and of the adenovirus vector. This led to the formation of so-called replication competent adenovirus (RCA), which is a safety related concern when E1-deleted adenovirus is to be administered to humans, *e.g.*, in gene therapy. RCA basically contains E1-sequences that were 'rescued' from the genome of the complementing cells. Fallaux et al. is directed to solving this problem, by providing a combination of a novel packaging cell and an E1-deleted adenovirus vector, which vector does not have overlap with the E1 sequences in the genome of the packaging cell. The packaging cells of Fallaux et al. are characterized in that they contain in their genome nucleic acid encoding the adenovirus E1A and E1B proteins but not pIX sequences, which enabled the formation of a packaging cell combined with a recombinant E1-deleted adenovirus vector without overlap and hence without forming RCA. The most preferred cell exemplified in Fallaux et al. for this purpose was the PER.C6™ cell. Clearly, Fallaux et al. relates to teaching a solution for preventing the problem of RCA generation when propagating recombinant E1-deleted adenovirus, and the characterizing feature of the PER.C6™ cells disclosed in Fallaux et al. is the presence in the genome of nucleic acid encoding E1A and E1B but not pIX protein, therewith solving that problem.

Fallaux et al. is therefore related to solving that specific adenovirus-related problem of the formation of RCA, and it is submitted that there is not a single sentence in Fallaux et al. that mentions or even remotely suggests the use of the packaging cells disclosed therein for the purpose as presently claimed, *i.e.* for the production of recombinant proteins.

Hence, the Fallaux et al. reference is considered to be in a different field, and will not provide suggestion or motivation to the skilled person that the cells disclosed therein, such as the PER.C6™ cells, would be useful in the production of recombinant proteins (*i.e.*, in the absence of production of adenovirus).

As previously described, Fallaux et al. further discloses on page 31 line 25 to page 32 line 2 that the cells therein (including PER.C6™ cells) were transfected with foreign DNA, using the *E. coli* β-galactosidase-encoding lacZ gene as a reporter. However, the transient transfections described therein did not include integration of the reporter gene into the genome of the cells, and therefore the disclosures therein do not teach or suggest all claim limitations of amended claim 1. In addition, applicants point out that this passage relates to transfections solely for the purpose of assessing whether the cells could take up DNA to assess the possibility to generate recombinant adenovirus in those cells (after the word "Therefore" in line 35, page 31), and therefore this passage is to be read by the skilled person in its context, which is to assess whether those cells were suitable for making recombinant adenovirus. Hence, this passage does not render obvious the present invention, relating to recombinant protein production in the absence of adenovirus proteins.

It is submitted that this passage, in view of the complete disclosure and context of the Fallaux et al. reference, and in the absence of the disclosure and teachings of the present invention, at the priority date of the present invention, would not be combined by the skilled person in an obvious manner with art that relates to recombinant protein production. Further, there was no motivation to make such combinations prior to the present invention.

In order to more closely define the invention, the element of claim 6, *i.e.* that the cells are of human embryonic retinoblast origin, has been incorporated into claim 1. Clearly, the PER.C6™ cells are the most preferred embodiment, and the advantages mentioned above have been exemplified with the PER.C6™ cells. In order to refrain from unduly limiting the scope of the invention and to claim the protection they feel entitled to based on the contribution to the art,

applicants claim cells of the same origin and also having adenovirus E1A and E1B sequences, for this purpose of recombinant protein production. It is submitted that the PER.C6™ cells can be viewed as exemplary for this cell type, see *e.g.,* Fallaux et al., where several related cells were established, see *e.g.,* page 29 line 33 to page 30 line 4. Therefore, the skilled person will know how to obtain such cells and in view of the present invention can test and use them for recombinant protein production in a manner analogously as disclosed and exemplified for the PER.C6™ cells in the specification of the present application.

The arguments above show that the skilled person had no reason to combine the Fallaux et al. reference with other prior art that related to protein production, since Fallaux et al. is completely silent on protein production, but rather pertains to adenovirus production. Already for these reasons the novel use of the PER.C6™ cells in the field of protein production is submitted to be non-obvious.

However, apart from this, it is submitted that Dorai et al., cited by the Examiner as secondary reference, would not lead the skilled person to the use of the PER.C6™ cells for recombinant protein production.

Dorai et al. discusses that it is not that straightforward to recombinantly produce a protein in host cells, see *e.g.*, column 1 lines 37-44, and column 12 lines 46-51 (the latter providing a kind of 'wish-list' for a suitable cell; it is submitted that fulfilling the criteria of the wish-list is to be confirmed after a cell has been identified and tested for this purpose, and could not be *a priori* known for the cells as currently claimed). It would therefore appear an oversimplification to simply combine any E1A expressing cell with Dorai et al. and state that it was obvious to use it, in the absence of an indication that a given cell type would be suitable for recombinant protein production. Rather, the full teaching of Dorai et al. should be taken into account, including the teachings cited therein, such as those of Cockett et al. (EP 0378,382, see column 3 lines 26-36 and column 13 lines 33-45; US Patent 6,653,101 is a family member of EP 0378,382 and has already been cited in the IDS and is therefore used for further reference herein). Cockett et al. (US Patent 6,653,101) discloses that optimization of the expression level of the transactivator (*e.g.,* E1A) is essential for obtaining a commercially useful level of the desired protein (which is for instance under control of a CMV promoter), that too much expression of transactivator (E1A) is inhibitory to cell growth, and that results of transient expression systems cannot be used to

predict the levels in stable cell lines (see Cockett, column 6 line 62 to column 7 line 17). Cockett thus suggests that E1A should preferably not be expressed at a too high level, in order to be beneficial in stable cell lines for transactivation of for instance a CMV promoter, and at least for CHO cells teach that the production of E1A should preferably be between about 10-40% of the expression of E1A in 293 cells. In contrast, PER.C6™ cells express E1A at a level that appears higher than that of 293 cells (see Fallaux et al., Figure 7), and hence it is at least not obvious to use the PER.C6™ cells for protein production in view of the teachings of Cockett et al. (the teaching would in fact appear in the opposite direction), which are followed in Dorai et al. (see *supra*, and further also Dorai et al. column 11 lines 40-51).

Indeed Dorai et al. provides an alternative to the teachings of Cockett et al., which alternative is presented as preferred, and which comprises the simultaneous co-transfection of the activator gene (*e.g.,* E1A) with the reporter gene (the nucleotide sequence encoding the protein of interest), and then to find the optimal clone (see Dorai et al., column 13 lines 33-45; see also Figure 1, column 9 lines 40-57). This would also not make obvious the present invention, wherein a PER.C6™ cell, which already expresses E1A (at a high level) and E1B, is transfected with the gene of interest and used for recombinant protein production. In addition, the contribution of Dorai et al. over the prior art could mainly be seen in providing for a further element in the cells (besides for instance a CMV promoter and E1A transactivator), *viz.* a second viral effector in the form of a translation activator such as the adenovirus VA1 gene, which appears to give a further increase in expression according to Dorai et al. (see *e.g.,* claim 1 in Dorai et al., column 8 lines 20-29, 32-35, Figure 1, column 9 line 44-46, column 11 lines 11-23, column 12 lines 13-17, column 13 lines 46-50, and all examples). The person skilled in the art would read Dorai et al. and follow the teachings to include this element for good protein production.

PER.C6™ cells do not comprise this element and are used without this element for high yield protein production. In addition, the process for producing proteins with PER.C6™ cells appears simpler in that it can easily be done by introducing only the desired gene of interest into the cells, rather than three different sequences simultaneously as preferred by Dorai et al. Further, Dorai et al. teaches for preferred embodiments that the gene of interest is amplified in the host cells (see *e.g.,* Dorai et al., column 4 lines 34-37, column 8 line 36-40, column 9 line 45,

column 11 lines 57-61, column 14 lines 52-67, examples 5+6). PER.C6™ cells do not need amplification steps for high yield protein production.

Although Dorai et al. provides a general indication that any eukaryotic cell lines that can be immortalized without significant reduction in growth rate or protein production can be used (Dorai et al., column 12 lines 44-46; it is noted again that the latter can only be known after the cell line has been used for the purpose of protein production, and hence cannot be viewed as making the use of PER.C6™ cells for this purpose obvious prior to the present invention), several preferred cells are mentioned, including the widely used CHO and myeloma cells such as NS0 and Sp2/0, which are also used in the examples, and no pointers to the presently claimed HER cells are given, so that the skilled person based upon Dorai, et al. would use the mentioned cell types that were known for their advantageous properties in the field of protein production, rather than use a cell that was not known to be useful in this field. 293 cells are mentioned as useful in transient cell systems (column 12 lines 36-38 and example 8, and appears to be used for finding optimal candidate vectors (see *e.g.,* column 21 line 13 and 41), which are contemplated to subsequently be transfected into desired cell types such as CHO (see column 21 lines 41-45). In addition, 293 cells are derived from kidney cells and hence will not make obvious the use of cells derived from retina cells that thus have a completely different origin, for recombinant protein production. Thus again, no incentive to produce a protein in E1-immortalized HER cells can be found in Dorai et al.

Moreover, Dorai et al. teaches away from human cells and thus from the cells as claimed (human embryonic retina cells), by stating: "Where cell lines are to be used to produce a biological intended for administration to humans, the host cell preferably is not a human cell line." (Dorai et al., column 8 lines 57-59).

In summary, the complete teachings of Dorai et al. should be read in their full context, and upon doing so it is submitted that Dorai et al. does not make obvious the use of the cells as claimed in the present invention. Moreover, there appears no motivation for the skilled person prior to the present invention to combine Fallaux et al. with Dorai et al.

The references do not teach or suggest all the claim limitations

The field of propagating recombinant adenovirus vectors is completely unrelated to the field of the current invention, being production of proteins (on industrial scale). It is for instance fully clear from the wording of the instant claims that the production of adenovirus is outside the present invention: the claims for instance recite that the eukaryotic cell 'does not express a structural adenoviral protein', whereas the teachings of Fallaux et al. are to use the cells as packaging cells for the propagation of adenovirus, which by necessity means that the cells in that case do express structural adenoviral proteins, since otherwise no adenovirus would be produced. Dorai et al. does not provide extra teachings to fill the void of the teachings of Fallaux et al. Therefore, the combination of Fallaux et al. and Dorai et al. would not suggest all the claim elements.

In summary, a *prima facie* case of obviousness has not been established for claim 1. Claims 2-6 have been canceled and thus rendering the rejections as to them moot. Claim 7-10, and 17-20 are not obvious over Fallaux et al. in view of Dorai et al. for, *inter alia*, depending from nonobvious claim 1.

Secondary considerations

The Supreme Court in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966), stated:

> Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or non-obviousness, these inquires may have relevancy. . .

The present invention for the first time discloses the novel and non-obvious use of the E1-immortalized HER cells for the purpose of recombinant protein production. These cells are particularly suitable for this purpose, which could not have been foreseen before the present invention.

Indeed, the PER.C6™ cells are highly suitable for production of proteins, as for instance is corroborated by a recent review (Yallop et al., 2005, PER.C6 cells for the Manufacture of Biopharmaceutical Proteins, In: Modern Biopharmaceuticals, Edited by J. Knäblein, WILEY-VCH Verlag GmbH & Co). For instance, the cells can be adapted to serum-free culture media

very simple and fast, which gives them the advantage that generation of production cell lines is typically quite short (see *e.g.*, Yallop, paragraphs 3.3.3, 3.3.5 and 3.7.1). They do not need amplification of the transgene in order to obtain high levels of protein production (see *e.g.*, Yallop, paragraphs 3.3.2, 3.3.5 and 3.7.1), therewith giving further advantages over systems where amplification is used, both in that less time is needed for the selection of appropriate PER.C6™ cells, and in that the generated cells do not suffer from the instability that can be associated with the high copy numbers found in amplified cell lines used in other systems. They can be suitably used in batch, fed-batch or perfusion production modes (see *e.g.*, Yallop, paragraphs 3.4 and 3.5). They can grow to very high cell densities, and cell concentrations achieved with this cell line appear to be the highest reported values to date for mammalian cell lines, which leads to very high product yields in perfusion systems (see *e.g.*, Yallop, paragraphs 3.5.3 and 3.7.2). The glycosylation profile of for instance produced IgG1 antibodies show a similar glycosylation profile to human serum IgG, and therewith favorably compares to antibodies produced in the widely used CHO cells (see *e.g.*, Yallop, paragraphs 3.6.3 and 3.7.3). Expression has been found to be stable (see *e.g.*, Yallop, paragraph 3.7.1). Moreover, yields of expressed proteins can be very high, *e.g.*, a fed-batch culture has yielded more than 3 g/l of recombinant antibody (see *e.g.*, Yallop, paragraph 3.4), which is in the same order of magnitude as found with the well-studied and much industrially used CHO cells (see *e.g.*, Yallop, paragraph 3.7.2), and which is thus considered very high and unexpected prior to the present invention.

Indeed, Applicant has already concluded more than 15 licenses for use of these cells in the field of recombinant protein production, in return for financial consideration. The licensed parties are based in different geographical areas, and include some of the world larger biotechnology and pharmaceutical companies. Hence, the invention embodies a clear commercial success. This can be seen as a further indication for non-obviousness of the invention.

Accordingly, applicants respectfully request the Office consider the secondary factors for the present invention.

CONCLUSIONS

Applicants believe that the amended claims are now allowable, and a notice of allowance is kindly solicited. If questions remain after consideration of the foregoing, the Office is kindly requested to contact applicants' agent at the address or telephone number given herein.

Respectfully submitted,

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Date: May 24, 2006
LF/bv

Enclosures: Replacement Sheets of Drawings
Annotated Sheets Showing Changes
Budapest Treaty Declaration
Deposit Receipt
Terminal disclaimer
Supplemental Information Disclosure Statement

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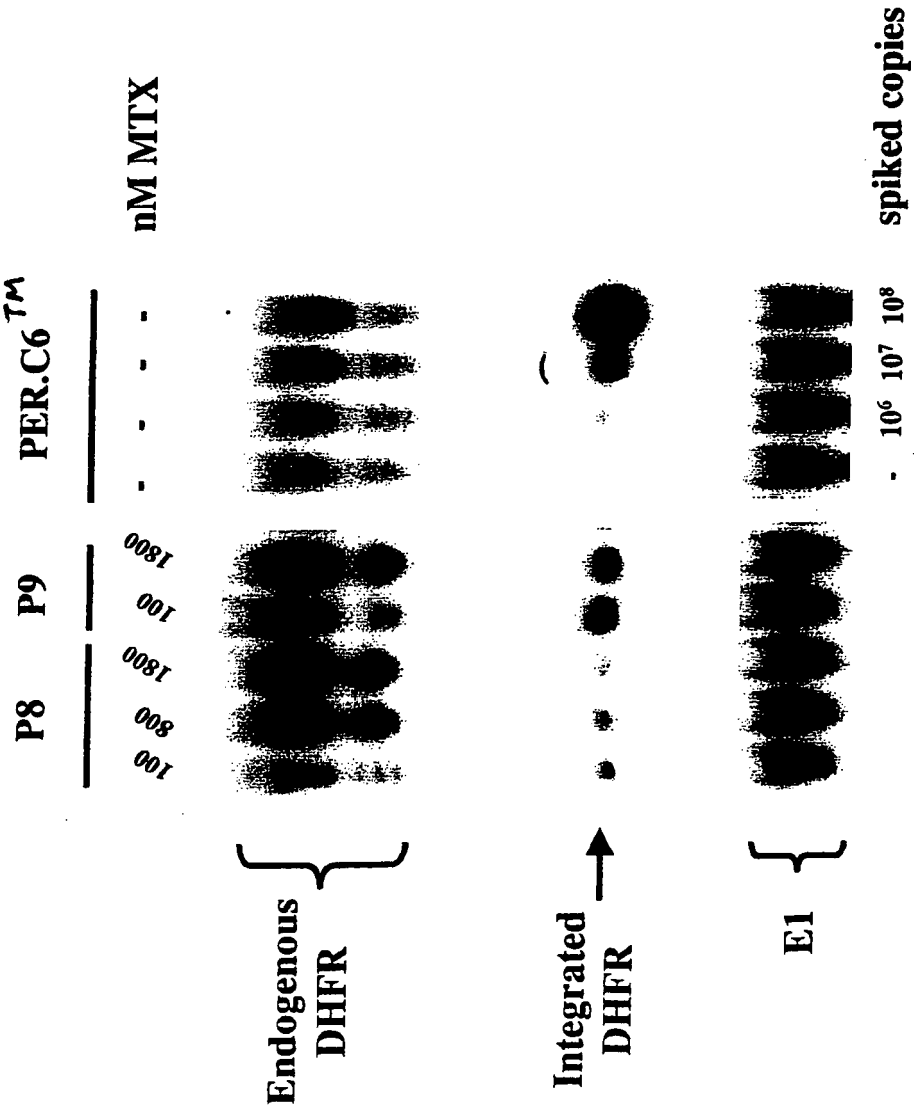
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Endogenous DHFR
Integrated DHFR
E1

FIG. 19

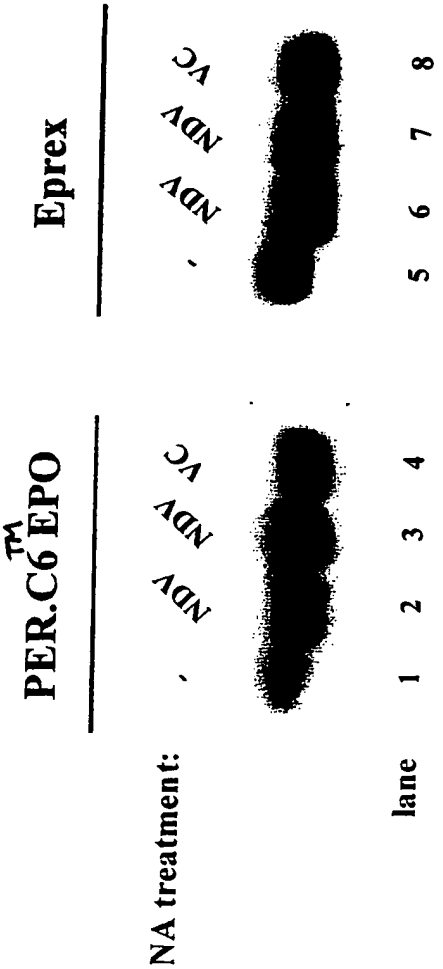

FIG. 21A

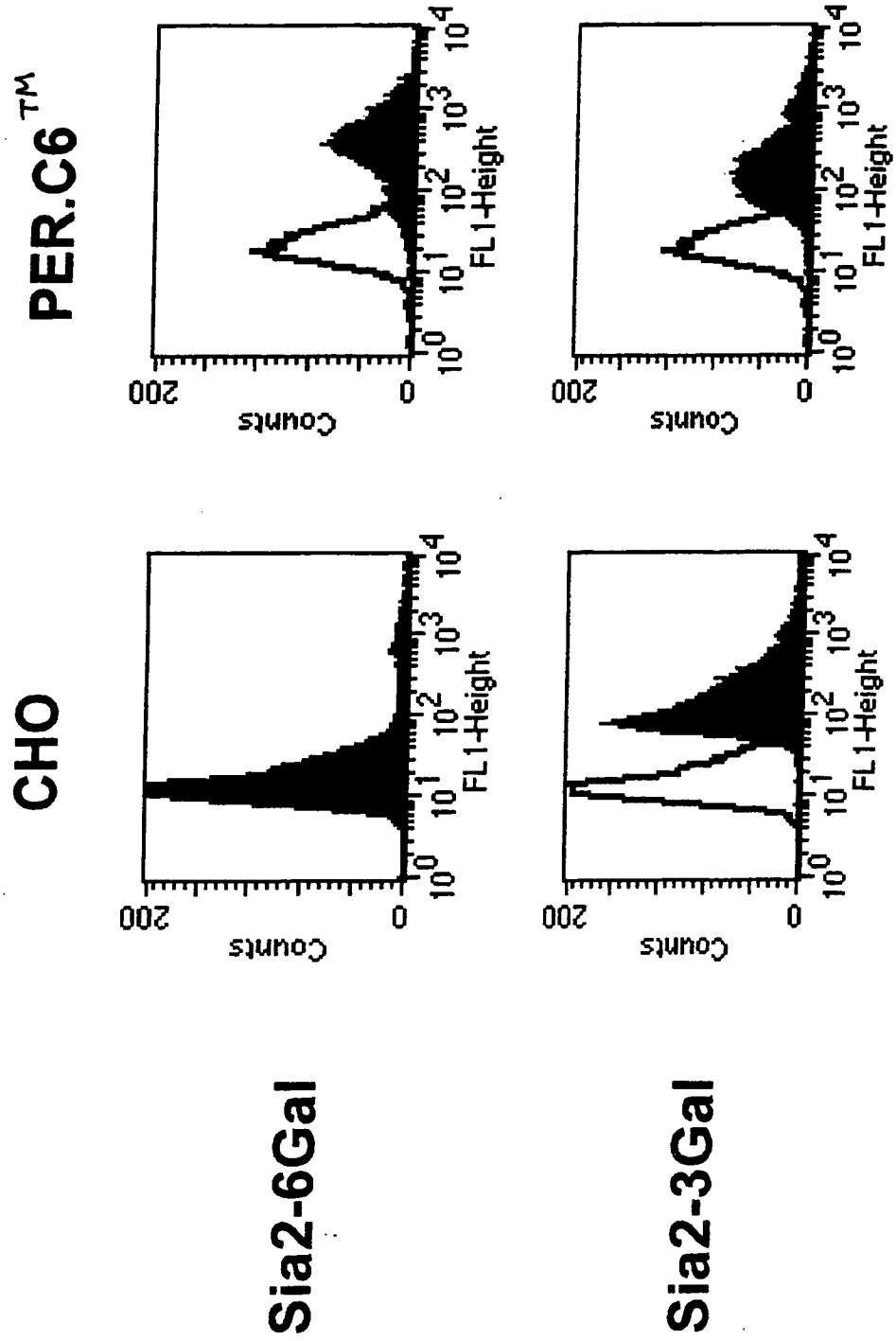
PER.C6™
CHO
Sia2-6Gal
Sia2-3Gal
Counts
FL1-Height
0
200
10^0
10^1
10^2
10^3
10^4

FIG. 21B

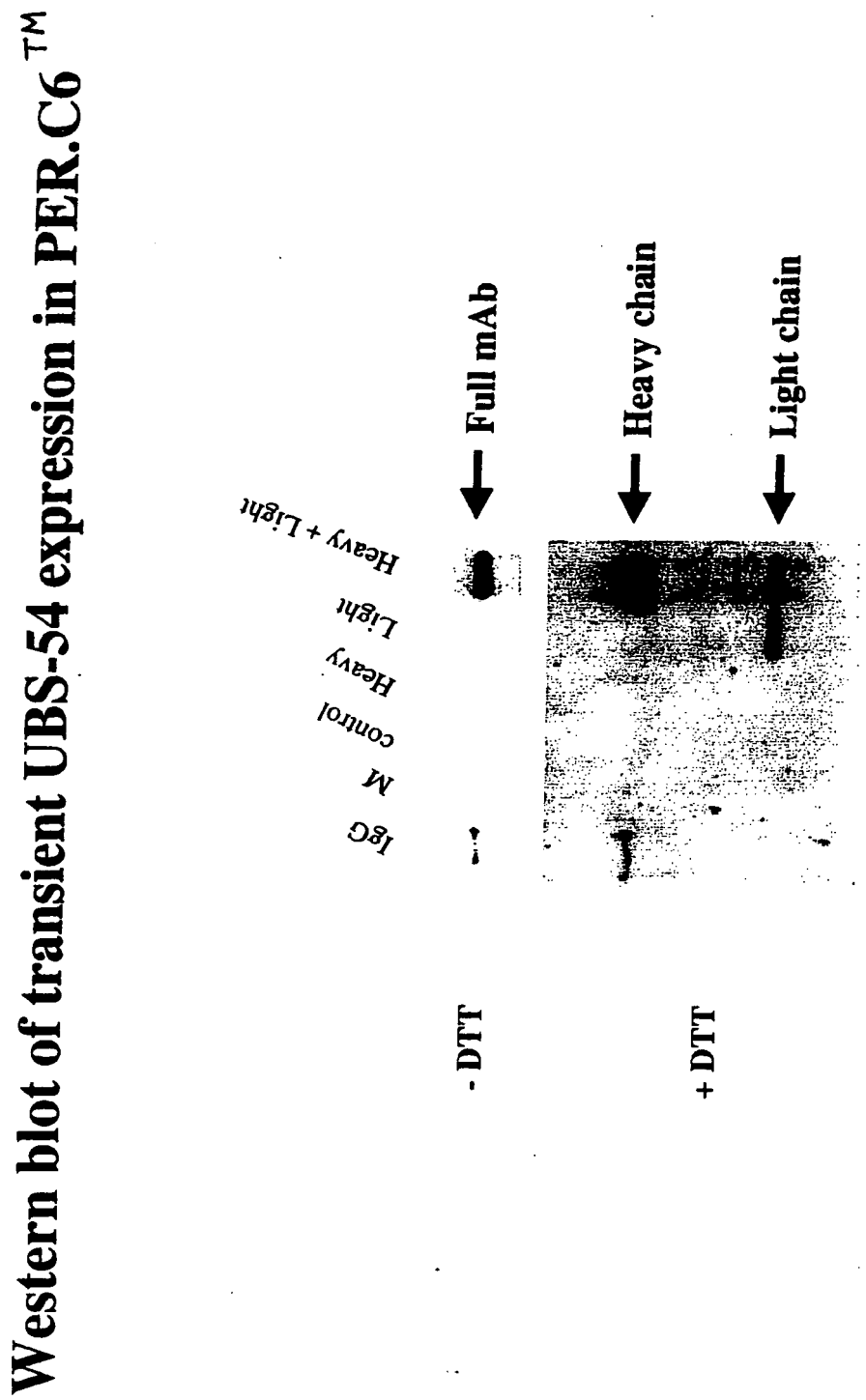
Western blot of transient UBS-54 expression in PER.C6™
Full mAb
Heavy chain
Light chain
Heavy + Light
Light
Heavy
control
M
IgG
- DTT
+ DTT

FIG. 24